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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,249	06/23/2006	Tomoyoshi Ishikawa	081356-0261	1542

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EXAMINER	
KIM, YUNSOO	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,249	ISHIKAWA ET AL.	
	Examiner	Art Unit	
	YUNSOO KIM	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-23 are pending.

2. Applicant's election without traverse of Group I, claims 1-21, drawn to a stable liquid medical formulation is acknowledged.

Accordingly, claims 22-23 are withdrawn from further consideration by the examiner under 37CFR 1.142(b) as being drawn to a nonelected invention.

Claims 1-21 drawn to a stable liquid medical formulation are under consideration in the instant application.

3. Applicant's claim for foreign priority under 35. U.S.C. 119 (a)-(d) is acknowledged.

4. Applicant's IDS filed on 6/23/06 is acknowledged. However, the foreign references A2-A13 have not been considered as Applicant has not provided the references.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 15-18 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a stable liquid medical formulation comprising an antibody wherein the antibody is IgG or any IgG subclasses such as IgG1, IgG2 or IgG4 **without** sequence modification, does not reasonably provide enablement for a stable liquid medical formulation comprising the IgG subclass with "**a part of**" which sequence has been subject to any "amino acid deletion, substitution and/or insertion by partial gene alteration" as in claim 15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed.Cir.1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of the skilled in the art to practice the claimed invention.

The claimed invention encompasses a stable antibody formulation wherein the antibody comprises any IgG subclasses with or without sequence modifications in constant or variable region of the antibody. As described in the U.S. Pat. No. 6,171,586 in cols 7-9, the antibody comprises of an antigen binding fragment (Fab: Variable region and CH-1) and Fc region (constant region) which involves in complement/effector function.

There is insufficient guidance in the specification as filed as to how the skilled artisan would make amino acid deletion, substitution and/or insertion by partial gene alteration of the antibody amino acid sequence as recited in claim 15. A person of skill in the art would not know which amino acids are essential, which amino acids are non-essential, and what particular lengths are essential to maintain the function of the antibody. There is insufficient guidance to direct a person of skill in the art to select particular amino acid is essential for antigen binding. Without detailed direction as to which amino acid is essential to antigen binding, a person of skill in the art would not be able to determine the antigen binding without undue experimentation.

The phrase "a part of" as in claim 15 is not limited to the constant region of antibody but it reads on the antibody comprises a constant region so the alteration of the amino acid sequence expands to variable region which involves in antigen binding as well as the constant region (Fc) which plays complement/effector function.

Reddy et al (The Journal of immunology, 2000, vol. 164, p. 1925-1933) teach that two single amino acid residue substitutions in the constant region of IgG4 ablate Fc binding activity (abstract, discussion, p. 1932). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single

amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that the antibody as defined by claim 15 which contains altered amino acid sequence would maintain the function of the antibody fragments. Therefore, the sequence modifications in constant region as well as the variable region affect binding of the antibody.

Furthermore, Applicant has no working examples demonstrating such modifications of sequences reserve the function of antibody or antibody fragments. Moreover, the claimed invention encompasses the sequence modification in DNA level as recited in the phrase "by partial gene alteration". It is unpredictable to deduce the nucleotide sequences when there is insufficient guidance in the specification as to how to determine amino acids to select for modifications without altering the function of antibody.

To summarize, reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breath of the claims, it would take undue trials and errors to practice the claimed invention.

7. Claims 15-18 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a stable liquid medical formulation comprising an antibody wherein the antibody is IgG or any IgG subclasses such as IgG1, IgG2 or IgG4 without sequence modification; however, applicant is not in possession of a stable liquid medical formulation comprising the IgG subclass with "a part of" which sequence has been subject to any "amino acid deletion, substitution and/or insertion by partial gene alteration" as in claim 15.

.

Given that the size of the constant region of the heavy chain antibody comprises more than 252 amino acids (Fig. 1, Reddy, p. 1926), the amino acid deletions, substitutions and/or insertion by partial gene alteration without considering variable light and heavy chains and constant light chain comprises a huge number of combinations of modified amino acids. The specification fails to disclose any species encompassed by the large genus of the antibody sequences. Consequently, conception in either case

cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-15, 18 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Pat. No. 6,171,586 B1.

The '586 patent teaches a stable aqueous pharmaceutical antibody formulation comprising an antibody in a citrate buffer at pH 4.5-6 (col. 6, lines 61-col. 7, lines 3, col. 5, lines 50-65). The '586 patent teaches the formulation prefers no addition of NaCl (col. 22, lines 31-35), but prefers addition of sorbitol as an isotonizing agent (e.g. tonifier, col. 6, line 52) and addition of polysorbate 80 as a surfactant (col. 22, lines 49-55). The referenced term "pharmaceutical" is interpreted to mean the claimed "medical".

Moreover, the '586 patent teaches the antibody is humanized, monoclonal antibody or chimeric antibody (col. 13-17). Claims 13-14 are included in this rejection as the purification methods of said antibody differentiate IgG1-4 and the resultant antibodies are IgG1-4 (col. 21, lines 41-65). Claim 15 is included in this rejection because a fusion of antibody with different constant and variable domains is available (col. 15-16, overlapping paragraph). The '586 patent further teaches the use of EDTA as a stabilizer (col. 23, lines 11).

The '586 patent teaches that the antibody formulation comprising a buffer, surfactant and stabilizer improves stability (col. 1, lines 15-40, col. 5-6, overlapping paragraph) and this formulation works for antibody formulation of many targets (col. 10, lines 5- col. 11, lines 14).

Furthermore, the '586 patent teaches that the buffer concentration is 1-50mM (col. 22, line 26), the concentration of the antibody is 2mg/ml to 10 mg/ml (col. 22, line 16), the concentration of surfactant (polysorbate 80) is 0.01% (col. 22, lines 49-60) and the osmotic pressure is between 250mOsm and 350mOsm (col. 6, lines 32-36). The percent concentration of 1g/100ml is 1%, the 0.01% of polysorbate 80 is equivalent to 0.1mg/ml. Therefore, the reference teachings anticipate the claimed invention.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-15 and 17-21 are rejected under 35 U.S.C. 103 as being unpatentable over U.S. Pat. No. 6,171,586B1 in view of U.S. Pat. No. 5,677,165.

The '586 patent has been discussed, supra.

The '586 patent does not teach use of glutamate as in claims 1, 19-20 and the use of CD-40 antibody as in claim 17.

However, the '165 patent teaches the antibody specific to CD40 and addition of glutamate in other buffer system to minimize pH change (col. 7, lines 41-50).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add glutamate and employ CD40 antibody as taught by the '165 patent to the antibody formulation taught by the '586 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the substitution of the CD-40 antibody to the antibody formulation taught by the '586 patent improves overall stability of the antibody and the addition of glutamate into other buffer system minimizes the pH change of the antibody solution.

From the teachings of references, it would have been obvious to one of ordinary skill in art to combine the teachings of the references and there would have been a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of the ordinary in the art at the time of invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 6,171,586 B1 in view of U.S. Pat. No. 5,677,165 as applied to claims 1-15, 18-21 above, and further in view of U.S. Pat. 6,416,958B2.

The '586 patent and the '165 patent have been discussed, supra.

The '586 patent or the '165 patent does not teach a HLA-DR antibody as in claim 16.

However, the '958 patent teaches a therapeutic composition comprising a HLA-DR antibody (col. 11, lines 35-54).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the stabilizing formation taught by the '586 patent and the '156 patent into a HLA-DR antibody taught by the '958 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the formulation taught by the '586 patent and the '165 patent improve stability of the antibody formulation and minimize pH change.

From the teachings of references, it would have been obvious to one of ordinary skill in art to combine the teachings of the references and there would have been a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of the ordinary in the art at the time of invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. No claims are allowable.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to YUNSOO KIM whose telephone number is (571)272-3176. The examiner can normally be reached on M-F,9-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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